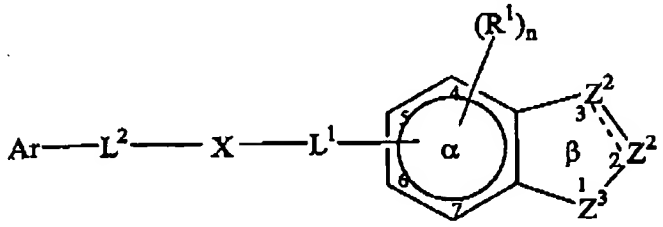
Application No.: 09/989,991 Docket No.: 219002029100

CLAIM AMENDMENTS

1. (currently amended) A compound of the formula:

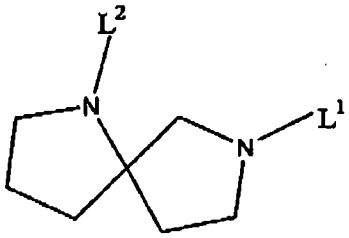


(1)

and the pharmaceutically acceptable salts thereof wherein:

Ar is an aryl group substituted with 0-5 ~~non-interfering~~ substituents selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, ~~heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl~~, NH-aroyl, halo, OR, NR_2, SR, SOR, SO_2R, OCOR, NRCOR, $NRCONR_2$, NRCOOR, $OCONR_2$, RCO, COOR, ~~alkyl-OOR~~, SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, R_3Si, and NO_2, wherein each R is independently H, alkyl, alkenyl or aryl ~~or heteroforms thereof,~~ and wherein two of said optional substituents on adjacent positions can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members;

L^2-X-L^1 is of the formula:



L^1 is CO, SO_2 or alkylene (1-4C);

L^2 is alkylene (1-4C) or alkenylene (2-4C) optionally substituted with one or two moieties selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, NH-aroyl, halo, OR, NR_2, SR, SOR, SO_2R, OCOR, NRCOR, $NRCONR_2$, NRCOOR, $OCONR_2$, RCO, COOR, alkyl-OOCR, SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, and R_3Si, wherein each R is independently H, alkyl, alkenyl or aryl ~~or forms thereof containing 1-2 O, S and/or N atoms,~~ and wherein two substituents on L^2 can be joined to form a non-aromatic saturated or unsaturated

ring that includes 0-3 heteroatoms which are O, S and/or N and which contains 3 to 8 members or said two substituents can be joined to form a carbonyl moiety or an oxime, oximeether, oximeester or ketal of said carbonyl moiety;

n is 0-3;

each R^1 is independently halo, alkyl, ~~heteroalkyl,~~ OCOR, OR, NRCOR, SR, or NR2, wherein R is hydrogen, alkyl, or aryl~~, or forms thereof containing 1-2 O, S and/or N~~;

$\diagdown\!\!\!\!\diagup$ represents a single or double bond;

one Z^2 is CA or CR^2A; the other Z^2 is CR^3, CR^3_2, NR^4 or N; and each R^2, R^3 and R^4 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, ~~heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl,~~ NH-aroyl, halo, OR, NR_2, SR, SOR, SO_2R, OCOR, NRCOR, $NRCONR_2$, NRCOOR, $OCONR_2$, RCO, COOR, ~~alkyl-OOR,~~ SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, R_3Si, and NO_2, wherein each R is independently H, alkyl, alkenyl or aryl ~~or forms thereof containing 1-2 O, S and/or N~~ and two of R^2 and/or R^3 on adjacent positions can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members, or ~~R^2 and/or R^3 is =O~~ or an oxime, oximeether, oximeester or ketal thereof;

Z^3 is NR^5 or O; where R^5 is H or is optionally substituted alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, ~~heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl,~~ or is SOR, SO_2R, RCO, COOR, alkyl-COR, SO_3R, $CONR_2$, SO_2NR_2, CN, CF_3, NR_2, OR, alkyl-SR, alkyl-SOR, alkyl-SO_2R, alkyl-OCOR, alkyl-COOR, alkyl-CN, alkyl-$CONR_2$, or R_3Si, wherein each R is independently H, alkyl, alkenyl or aryl ~~or forms thereof containing 1-2 O, S and/or N~~;

A is $-W_i-COX_jY$, where Y is COR^6 or an isostere thereof, each of W and X is substituted or unsubstituted alkylene or alkenylene, each of 2-6Å; each of i and j is independently 0 or 1; and R^6 is H, or is straight or branched chain alkyl, alkenyl, alkynyl, aryl, arylalkyl, ~~heteroalkyl,~~ heteroaryl, or heteroarylalkyl, each optionally substituted with halo, alkyl, ~~heteroalkyl,~~ SR, SOR, SO_2R, SO_2NR_2, OR, NR_2, OCOR, NRCOR, $NRCONR_2$, $NRSO_2R$, $NRSO_2NR_2$, $OCONR_2$, CN, COOR, $CONR_2$, COR, or R_3Si wherein each R is independently H, alkyl, alkenyl or aryl ~~or forms thereof containing 1-2 O, S and/or N~~, or

wherein R^6 is OR, NR_2, SR, $NRCONR_2$, $OCONR_2$, or $NRSO_2NR_2$, wherein each R is independently H, alkyl, alkenyl or aryl ~~or the heteroatom-containing forms thereof,~~ and wherein two R attached to the same atom may form a 3-8 member carbocyclic or heterocyclic ring and wherein said ring may further be substituted by alkyl, alkenyl, alkynyl, aryl, arylalkyl, ~~heteroalkyl,~~ heteroaryl, heteroarylalkyl, each optionally substituted with halo, SR, OR, NR_2, OCOR, NRCOR, $NRCONR_2$, $NRSO_2R$, $NRSO_2NR_2$, $OCONR_2$, or R_3Si wherein each R is independently H, alkyl, alkenyl or aryl ~~or forms thereof containing 1-2 O, S and/or N~~ wherein two R attached to the same atom may form a 3-8 member ring, optionally substituted as above defined.

2. (canceled)

3. (original) The compound of claim 1 wherein Y is an isostere of COR^6.

4. (original) The compound of claim 3 wherein Y is tetrazole; 1,2,3-triazole; 1,2,4-triazole; or imidazole.

5. (original) The compound of claim 1 wherein each of i and j is 0.

6. (previously presented) The compound of claim 1 wherein j is 0.

7. (original) The compound of claim 1 wherein Z^3 is NR^5.

8. (canceled)

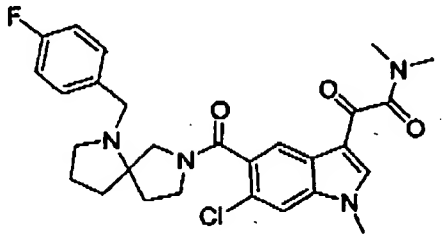
9. (previously presented) The compound of claim 1 wherein R^5 is H, or is optionally substituted alkyl or acyl.

10-11. (canceled)

12. (previously presented) The compound of claim 1 wherein R^2 and R^3 are independently selected from halo, OR and alkyl.

13-38. (canceled)

39. (previously presented) The compound of claim 1 wherein the compound is:



40. (currently amended) The compound of claim 1 wherein L^1 is CH_2 or CO and L^2 ~~are independently selected from CO, CHOH, CH_2 NH CO, CH_2 N CH3, and~~ is CH_2 or CHOH.

41. (currently amended) The compound of claim 40 wherein L^1 ~~and/or L^2~~ is CO.

42-44. (canceled)

45. (previously presented) The compound of claim 1 wherein L^2 and/or L^1 is unsubstituted alkylene.

46. (previously presented) The compound of claim 1 wherein L^2 and/or L^1 is unsubstituted methylene, or methylene substituted with alkyl.

47. (canceled)

48. (previously presented) The compound of claim 1 wherein Ar is optionally substituted phenyl.

49. (original) The compound of claim 48 wherein said optional substitution is by halo, OR, or alkyl.

50. (original) The compound of claim 49 wherein said phenyl is unsubstituted or has a single substituent.

51. (canceled)

52. (previously presented) The compound of claim 1 wherein R^1 is halo or alkoxy.

53. (original) The compound of claim 52 wherein n is 0, 1 or 2.

54. (original) The compound of claim 1 wherein L^1 is coupled to the α ring at the 4-, 5- or 6-position.

55. (original) The compound of claim 1 wherein Z^2 at position 3 is CA or CHA.

56. (original) The compound of claim 55 wherein the Z^2 at position 2 is CR^3 or CR^3_2.

57. (currently amended) The compound of claim 56 wherein R^3 is hydrogen, or is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, ~~heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl,~~ NH-aroyl, halo, OR, NR_2, SR, SOR, SO_2R, OCOR, NRCOR, $NRCONR_2$, NRCOOR, $OCONR_2$, RCO, COOR, ~~alkyl-OOR~~, SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, R_3Si, and NO_2, wherein each R is independently H, alkyl, alkenyl or aryl ~~or forms thereof containing 1-2 O, S and/or N~~ and two of R^1 can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members.

58. (currently amended) The compound of claim 57 wherein each R^3 is selected from the group consisting of H, alkyl, acyl, aryl, arylalkyl, ~~heteroalkyl,~~ heteroaryl, halo, OR, NR_2, SR, NRCOR, ~~alkyl-OOR~~, RCO, COOR, and CN, wherein each R is independently H, alkyl[[,]] or aryl ~~or forms thereof containing 1-2 O, S and/or N~~.

59. (original) The compound of claim 55 wherein Z^2 at position 2 is N or NR^4.

60. (currently amended) The compound of claim 59 wherein R^4 is H, or alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, ~~heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl,~~ or is SOR, SO_2R, RCO, COOR, alkyl-COR, SO_3R, $CONR_2$, SO_2NR_2, CN, CF_3, or R_3Si wherein each R is independently H, alkyl, alkenyl or aryl ~~or forms thereof containing 1-2 O, S and/or N~~.

61. (currently amended) The compound of claim 1 wherein ⟍ represents a double bond.

62. (canceled)

63. (currently amended) A pharmaceutical composition ~~for treating conditions characterized by enhanced p38 α activity~~ which composition comprises ~~a therapeutically~~ an effective amount of a compound of claim 1 and a pharmaceutically acceptable excipient.

64-67. (canceled)

68. (currently amended) [[~~The~~]] A method to treat ~~of claim 67 wherein said proinflammation response is multiple sclerosis, IBD,~~ rheumatoid arthritis, ~~rheumatoid spondylitis, osteoarthritis, gouty arthritis, other arthritic conditions, sepsis, septic shock, endotoxic shock, Gram negative sepsis, toxic shock syndrome, asthma, adult respiratory distress syndrome, stroke, reperfusion injury, CNS injury, psoriasis, restenosis, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, a bone resorption disease, graft versus host reaction, Crohn's Disease, ulcerative colitis, Alzheimer's or pyresis~~ which comprises administering to a subject in need of such treatment a compound of claim 1 or a pharmaceutical composition thereof.